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Ethical considerations in post-market-approval monitoring and regulation of vaccines

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ABSTRACT

The objective of this paper is to identify and articulate ethical considerations to help guide decision-making around the regulation and monitoring of vaccines post-licensure. While these considerations are not intended to be an exhaustive account of the ethical concerns, they can facilitate the explicit examination of ethical issues in this context. We identify the protection of public from harm as the primary consideration, and identify others that help in the discharging of this governmental obligation. Others include: transparency, a publicly acceptable risk-benefit profile, public trust, minimization of stigma, and special obligations to vulnerable populations. Regulators and researchers can use these ethical considerations to help enhance their reasoning and to improve the accountability of their decision-making. These considerations can be used to inform rational deliberations about how to balance the obligation to protect the public from harm with other relevant considerations such as the need to be transparent, while taking into account the contextual features of the situation. Further research and debate on the relevance and refinement of these ethical considerations is desirable.

1. Introduction

It has been over a decade since scholars began to articulate principles to guide the ethical analysis of issues in public health. Public health ethics is now a robust field of study including theoretical and practical considerations. However, there is a paucity of ethical analysis about the issues associated with pharmaceutical and vaccine regulation, particularly in the post-licensure context [1,2]. Risk-benefit analysis and policy-making are not a value-free enterprises, and involve important moral trade-offs. Often these ethical trade-offs are not explicitly articulated, and remain invisible. In this paper, we focus on the post-market monitoring of vaccines and identify ethical considerations arising from their monitoring and regulation. Many of the ethical considerations raised here will be relevant to the post-market monitoring of drugs as well, but not necessarily to the pre-authorization phase of regulation and research because of the distinguishing conditions of uncertainty and, at times, urgency [1] that obtain in the real-world setting of vaccine use.

In the last decade there has been a growing acknowledgement internationally that government bodies responsible for ensuring the safety and effectiveness of pharmaceuticals and vaccines face serious challenges when protecting the public from harm once these products are used by people in the uncontrolled, real-world context [4–7]. In most jurisdictions, regulation has been moving towards an approach that takes into account the full lifecycle of a drug or vaccine. This shift to lifecycle regulation has brought with it a more comprehensive surveillance mandate and sometimes progressive licensing legislation as well as the need for more evidence-generating capacity about how drugs and vaccines behave outside of clinical trials. In some jurisdictions, such as Canada, the shift to a lifecycle approach has been slow though, and there have been calls for further changes to how regulators safeguard the public's health and public healthcare resources [8].

Within this post-market regulatory context, public health agencies seek to increase vaccination uptake rates in the wake of a growing trend for particular groups to be hesitant about vaccination. Parents who refuse or hesitate to vaccinate their children have often chosen to focus more on the perceived risks of adverse events from vaccination than on the risks of vaccine-preventable diseases [9,10]. This trend has meant that vaccine

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safety is foremost in the minds of many, and requires that regulators do their utmost to ensure that vaccines are safe and effective and to engender the public's trust in the regulatory system. In addition, Verweij and Dawson have argued that vaccines should be held to higher standards of effectiveness and safety than other pharmaceutical products because most "vaccinations are offered to healthy individuals as a measure to prevent possible future harm" [11], especially in places where herd immunity is in effect and the chances of contracting diseases are low.

Given the recent shifts towards lifecycle regulation, and the increasing reach of regulatory authorities to compel pharmaceutical companies to conduct post-market research [12–15] this is an opportune moment to ask what kinds of ethical concerns regulators should be factoring into decision-making when it comes to ensuring post-market vaccine safety and effectiveness. The set of considerations articulated herein is not meant to explicitly address the more narrow sub-set of concerns that pertain to the ethical conduct of research on and surveillance of post-market vaccines, such as privacy, informed consent, etc. that have been considered elsewhere [16–18]. Rather, the focus is on ethical considerations for regulatory decision-making. First we shall articulate the considerations, and then discuss their role within post-market monitoring and regulatory context.

2. Identification of ethical considerations

The considerations articulated herein are the result of bioethical analysis of the post-market regulatory context of vaccine regulation in developed countries. In some cases, they are reformulations of accepted ethical principles discussed within the bioethics literature [11,19–21], and others are based upon bioethical analysis of recent controversies around vaccines and their safety and efficacy, such as the human papilloma virus vaccine (HPVV) [22–24]. While there has been important work done on the ethics of collective immunization programs [11,19], vaccine safety and effectiveness is either taken for granted as a starting point for the analyses, or identified as an ethical principle but not examined in depth. This paper provides a more detailed ethical analysis of what needs to be taken into consideration ethically when regulators are conducting post-market vaccine monitoring and regulatory activities. For it is often the case that when collective immunization programs are initiated, especially in emergency circumstances, vaccines have limited real world data to support the claim that they are safe and effective, and thus vaccination programs can function as de facto real-world vaccine trials [23]. It is therefore necessary to articulate some ethical considerations, especially for cases where groups that are underrepresented in pre-market clinical trials are the target of collective immunizations programs, such as was the case with the HPVV in Canada [22].

3. Ethical considerations

(1) Protection of the public from harm,
(a) highest quality of evidence possible,
(b) anticipatory decision-making,
(c) duty to warn,
(d) proportionate monitoring.
(2) Transparency,
(3) Publicly acceptable risk benefit profile,
(4) Minimization of stigma
(5) Special obligations to vulnerable populations,
(6) Public trust.

3.1. Protection of the public from harm

The need to ensure that vaccines do not harm people because of lack of safety or effectiveness is of paramount concern and is the primary norm upon which monitoring activities are based. This moral obligation is typically enshrined in the mandates of government health and regulatory agencies. Regulators must also ensure that harm is not caused by withdrawals of vaccines from the market or by other restrictions that can cause channeling to other unsafe drugs, vaccines or therapies [1], or by leaving special sub-populations without alternatives for prevention or treatment. The subsequent four ethical considerations should be considered as related to protecting the public from harms that can arise from both safety and effectiveness issues. They will not all always be relevant, and some may even be in tension with this consideration and thus they will need to be weighed carefully by regulators.

3.1.1. Highest quality of evidence possible

Anticipating where problems may arise with vaccines requires the gathering of the best quality of evidence possible for use in decision-making. In most cases, active surveillance and research on all vaccinated populations is preferable to relying on passive reporting, although under many regulatory systems this is seldom feasible. Hard end-points should be used in studies where possible to compensate for the problems associated with using soft end-points in pre-market clinical trials, even though this may require long-term surveillance in some cases [25]. The most ethically-relevant aspect of this consideration, however, is the need to minimize conflicts of interest that can introduce bias in research design and reporting. Research that informs regulation ought to have integrity: whenever possible, monitoring and research should be free from industry influence [26,27]. Evidence about the comparative effectiveness of a vaccine is also necessary to evaluate whether it is effective compared to existing vaccines or other preventive actions or therapies [11]. This is needed in order to minimize the technological imperative to use the newest technologies that can sometimes result in discarding other equally or more effective methods of preventing disease [28]. The sharing of safety and effectiveness data across jurisdictions is also required and should be facilitated by increasing the capacity to do so both within countries and between them.

3.1.2. Anticipatory decision making

Regulators should take a proactive role in shaping safety and effectiveness surveillance and research, and engage in preemptive decision-making in order to prevent harm. Precautionary actions such as withdrawal of a vaccine from the market, or the use of black box warnings must be proportionate to the degree of scientific certainty, the severity of possible harm, the size and nature of the affected population, and the cost of the actions [29,30]. Decisions should also be subject to review in light of new information [20]. Anticipatory decision making can be fostered by the collection of the highest quality of evidence possible. It should be noted, however, that the premature or complete withdrawal of a vaccine from the market can also cause harm under certain circumstances, and thus a precautionary approach may not always be ethically appropriate.

3.1.3. Duty to warn

Regulators have the duty to warn people when safety and/or effectiveness issues are present with a vaccine. This can include important reminders about waning immunity requiring a booster in order that people remain protected from disease. For vaccines where long-term effectiveness is unknown this is particularly important, because other measures such as screening may become even more important for people in order to prevent morbidity and

mortality. Warnings need to be communicated in a timely and appropriate manner. It must be noted, however, that the social context of immunization programs may be such that premature, or overly alarmist warnings may negatively impact vaccine acceptance in the population as a whole or in particular sub-populations. Thus, while there is a moral obligation to provide all relevant information about vaccine safety and effectiveness to the public in the interests of respecting individual autonomy and promoting informed consent, this must be balanced with the need to prevent the spread of disease. Thus, the burden of disease needs to be taken into consideration when warning the public of possible harm when evidence of harm is uncertain.

3.1.4. Proportionate monitoring

This consideration speaks to the need to ensure that monitoring activities are proportionate in scope to what is known about the risk-benefit profile of a particular vaccine, as well as to the vulnerability of the population being immunized (see Section 3.5 below). Also, the scale of use (is the vaccine being used in a collective immunization campaign?) should also be taken into consideration when deciding what kind of monitoring activities are necessary to protect the public from harm. Proportionality should inform decisions around whether active or passive monitoring is needed, and whether targeted or universal monitoring is needed.

3.2. Transparency

Transparency requires that the rationale for regulatory decisions, as well as the decisions themselves need to be communicated to the public. In addition, risk communication around safety issues with vaccines needs to be made accessible and understandable in a timely manner. Communicating to the public what is not known about the safety and effectiveness profile of a vaccine is as important, if not more important, than what is known [31]. Transparency requires that information be communicated in a way that can be understood by the public. The need to be transparent with the public is often thought to be in tension with the need to protect the public from the harm in that transparency might result in a decline in vaccine uptake. However, if public trust is damaged from a lack of transparency, vaccine uptake more broadly may be negatively impacted. Thus, there must be good reason for keeping safety and effectiveness information from the public, for regulators' mistrust of the public's ability to understand information relating to vaccine safety may result in a reciprocal mistrust in regulators on the part of the public [31,32]. Transparency with industry, however, around what vaccines may be undergoing further safety or effectiveness studies may compromise the independence (and therefore integrity) of such research [8].

3.3. Publicly acceptable risk-benefit profiles

The process of defining what constitutes a publicly-acceptable level of risk is a distinctly political responsibility and is one that is ultimately based on values and priorities. Because there can be small direct benefit to individuals due to a lower probability of contracting diseases where herd immunity has been achieved, there is a low public tolerance for risks associated with vaccination [10]. There is a corresponding responsibility, therefore to maximize the safety and effectiveness of a vaccine [11]. A high safety threshold for vaccines must be maintained in order to achieve acceptable levels of public uptake, especially for non-therapeutic vaccines. In public health emergencies, the public may be more likely to accept vaccines that have less evidence of safety and efficacy [23], but more stringent monitoring is required by the need for proportionate monitoring. In addition, comparative effectiveness requires that the vaccine present a risk-benefit profile that is preferable to other preventive modalities [11]. How to determine what is publicly acceptable might in part be a function of considering uptake levels, but in the case of compulsory vaccination this could be difficult, and requires careful attention to avoid the abuse of public health powers to compel individuals to be immunized.

3.4. Minimization of stigma

When public health agencies decide to put a population under surveillance or to conduct research on particular groups, it can potentially have a (re)stigmatizing effect on that population. Even though it may be less cost-effective, there may be circumstances where monitoring activities need to be less targeted in order to avoid the undue stigmatization of groups vulnerable to being singled out as different in some way [24]. This must be balanced with the need to collect enough detailed information to protect vulnerable groups from harm. Potentially stigmatizing research or surveillance can include but is not limited to the collection of data about vaccine uptake or acceptability and about behavioural responses to vaccines (particularly for those vaccines that might change behaviours that are themselves potentially stigmatizing, e.g. sexual behaviour).

3.5. Special obligations to vulnerable populations

The routine exclusion of particular populations from pre-market clinical trials creates a *prima facie* vulnerability in children, women, older people, and aboriginal peoples owing to fact that evidence of safety and effectiveness is often minimal or non-existent. In certain cases, it may be necessary to focus monitoring activities on these populations to determine if they are actually at greater risk of harm. Harm could be a direct result from an adverse event following immunization, diminished vaccine effectiveness, or behavioural change that puts them at risk of harm [10,34]. In addition, the risk-benefit ratio is not the same for all sub-groups in a population: differences in genotype and the health status of individuals can be reasonably expected to render some populations more at risk from adverse events and diminished effectiveness than others [10,33]. It may also be the case that their inability to mount an effective immune response to a vaccine also renders them more vulnerable to infection from the disease public health agencies are trying to prevent. In the common context of scarce resources and little capacity for post-market monitoring activities, this consideration could be used to justify the prioritization of surveillance and research on these populations, in order to mitigate this kind of vulnerability and in order to provide alternative protective measures where necessary. However, this obligation needs to be considered in light of the potentially stigmatizing effect of targeted monitoring activities.

3.6. Public trust

Many vaccinations are only effective if high levels of uptake are achieved in order to get the protective effect of herd immunity. This can only be accomplished if the public trusts public health actors and regulators and distrust can be engendered when the public feels that regulators and public health officials are not trustworthy. It is therefore important that conflicts of interest on the part of researchers involved in pharmaco-epidemiological research and regulators appropriately declare and manage conflicts of interest, and that regulators take account of the potential for bias in research findings by researchers with ties to industry [26]. Anticipatory decision-making engenders public trust, as opposed to reactive decision-making. Finally, being explicit about how decisions around vaccine safety and effectiveness are made and communicating with the public in a transparent fashion about the risks and benefits of vaccines is essential.

4. Discussion

Bioethical analysis of post-market vaccine monitoring and regulation reveals the tensions that can exist between ethical concerns. Clearly, while the protection of the public from harm is of paramount importance here, and a strong government responsibility, careful balancing of the types of harm that can occur beyond those directly related to vaccine safety and efficacy must occur. While we suggest that rational deliberation [21] must occur in order to ensure that the ethical tensions are acknowledged and addressed, we do not suggest that this set of considerations is exhaustive or decisive. The empirical context is directly relevant to bioethical deliberation, as there may be morally relevant facts that can inform how to weigh these considerations. Having said this, we agree with Verweij and Dawson that despite the fact that decisions are taken within a specific regulatory context in which there are empirical facts that need to be taken into account, "some agreement can be reached about which general norms should guide", even when agreement about the interpretation of the ethical considerations remains contested [11]. We thus propose these ethical considerations as a starting place for ethical reflection and as a means to fostering deliberation, not closing down discussion.

5. Conclusion

The utility of these considerations will require evaluation, as the conceptual nature of this research will require further refinement through empirical research and input from a community of scholars and regulators and the public [3]. It is hoped that these considerations will encourage regulators and researchers charged with the post-market monitoring of vaccines to consider the explicit articulation of values in the decision-making and research-shaping process in this context.

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Conflict of interest statement

We declare that we have no conflicts of interest, and that the funder (Canadian Institutes of Health Research) had no say in the design, interpretation or conclusions of this research.

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